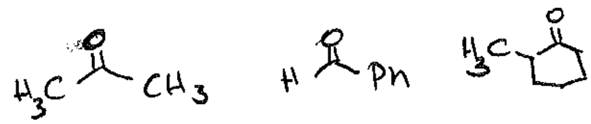
① LECTURE 16 : Asymmetric Catalysis

Computational Chem in December.
Midterm # 2 : Tues, Nov 3.
Comprehensive!

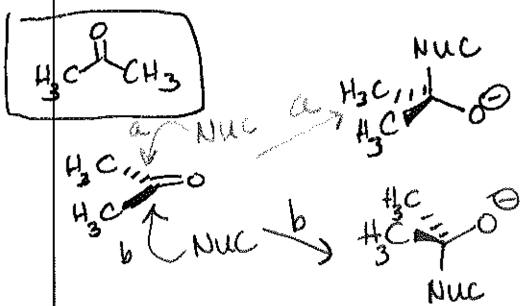
PS # 7 due Now.

Seminar : Douglas Buttrey
(UDel Chem Engineering)
Wed 4pm, 219 BRL.

②
Consider faces of an aldehyde or ketone :
Homotopic, Enantiotopic or Diastereotopic?
(Homotopic → same; Enantiotopic → enantiomer-making; Diastereotopic → diastereomer-making)

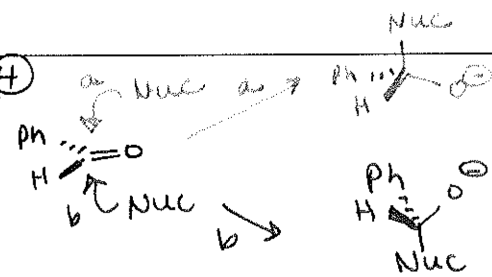


③ How to tell : Hypothetical nucleophile



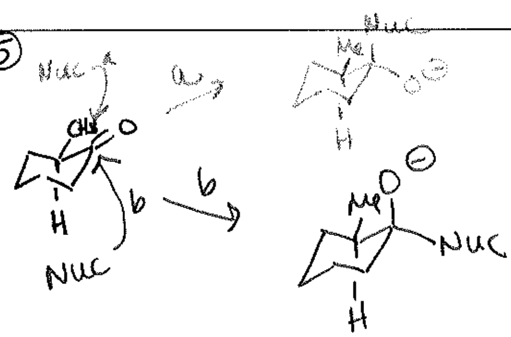
same, so HOMOTOPIC.

④



Enantiomers, so faces are ENANTIOTOPIC.

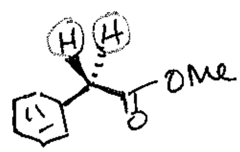
⑤



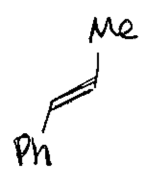
Diastereomeric Products, so faces are Diastereotopic.

Note: Racemic mixture of ketone OK. Each molecule still has 2 diastereotopic faces.

⑥ HOMOTOPIC, ENANTIOTOPIC, & DIASTEREOTOPIC CAN BE APPLIED TO OTHER FRAGMENTS:



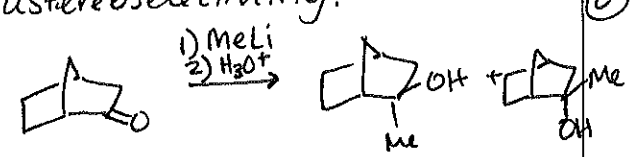
Enantiotopic protons ⇒ Replace one & you get enantiomers.



Enantiotopic olefin faces (add to one)

(7) Diastereoselectivity:

ex:

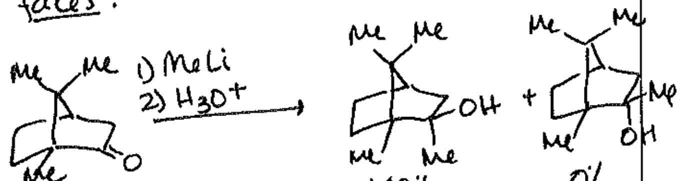


norbornanone — 0% — 100%

Chiral? Yes — (Diastereomers)

Diastereotopic faces.

ex:

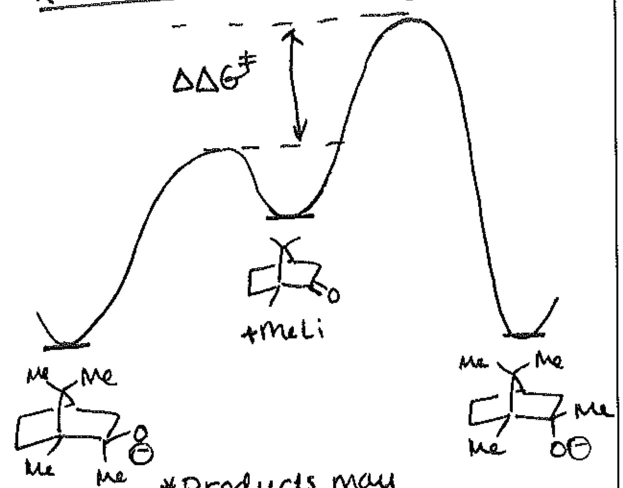


Camphor — 100% — 0%

Chiral? Yes. — (Diastereomers)

Diastereotopic faces.

(8) Rxn coordinate Diagrams:

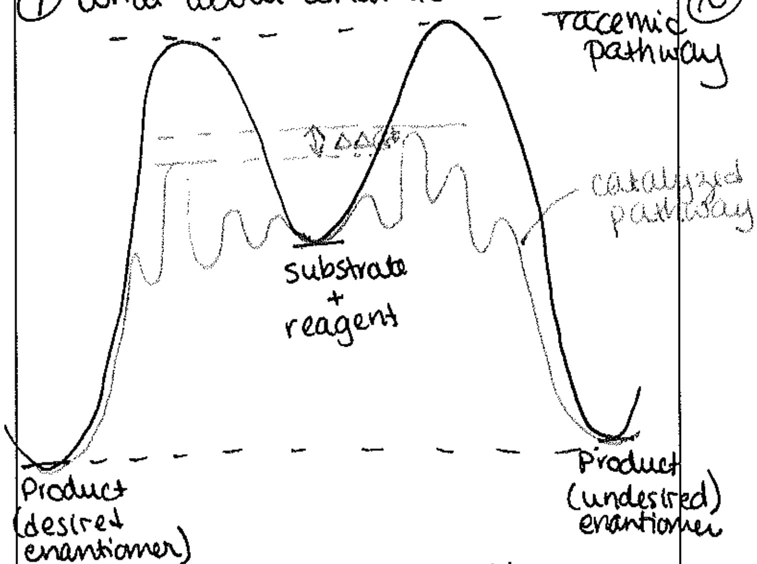


100% — 0%

*Products may or may not have same ΔG.

$\Delta\Delta G^\ddagger$ = difference in $\Delta G^\ddagger$'s.

(9) What about enantiomers?



Products are same ΔG!!

(10)

$\Delta\Delta G^\ddagger$ determines enantioselectivity!

temp (°C)	$\Delta\Delta G^\ddagger$ 90% ee	$\Delta\Delta G^\ddagger$ 99% ee
−78	1.1	2.1
25	1.7	3.1
100	2.2	3.9

"We live & die by 1 kcal."

(11)

But WHY are energy barriers different?

Catalyst must be CHIRAL.

⇓

STEREOCHEMICAL COMMUNICATION

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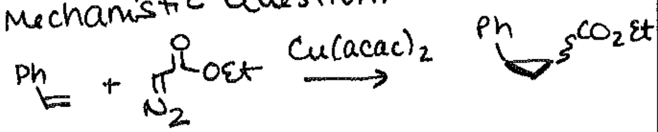
Birth of Asym. Catal.

Nozaki, Moriuti, Takaya & Noyori TL 1966, 43, 5239.

(Nobel 2001 : Knowles, Noyori, Sharpless)

Mechanistic Question:



What is Cu doing? Is it involved in C-C bond-forming step?

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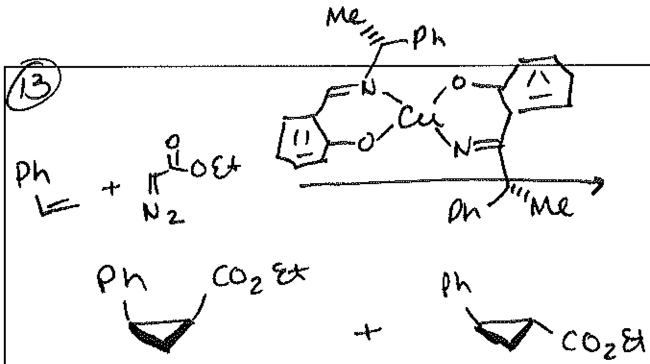
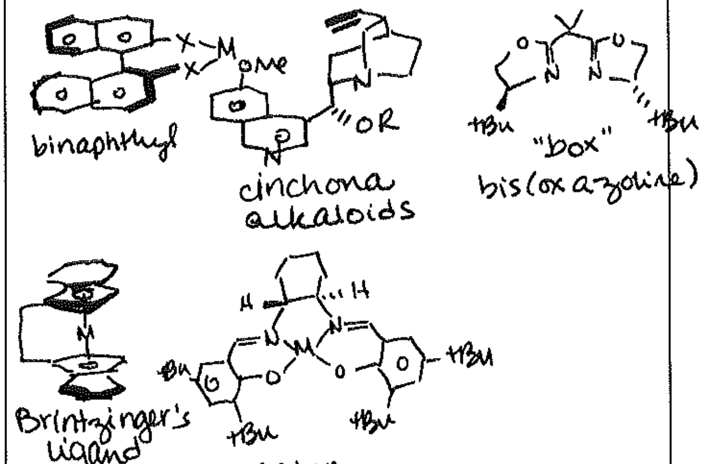


6% ee   6% ee

Chiral catalyst ⇒ Stereochemical communication w/ T.S.!!...

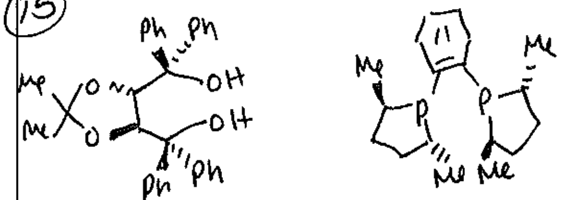
(14) We've come a long way...

"Privileged" Chiral Ligands



Yoon & Jacobsen. Science 2003, 299, 16..

(15)



TADDOL   DUPHOS (DUPont)

But how do these work?

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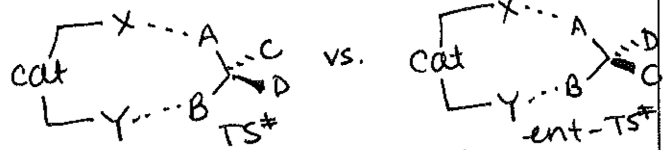
3-Point Rule for Chiral Recognition

(Pirkle Chem Rev 1989, 89, 347)

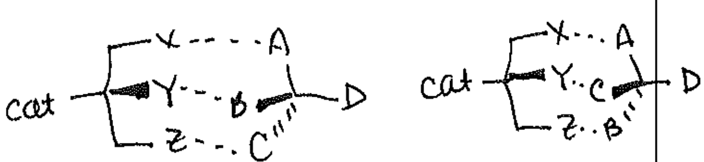
Chiral recognition requires ≥ 3 simultaneous interactions w/ ≥ 1 being stereochemically dependent.

Generically: 2 points = insufficient.



X & Y = "recognition elements"

(17) 3rd point in 3rd dimension:



TS‡   ent-TS‡

$\Delta G^{\ddagger} \neq \Delta G^{\ddagger}_{ent}$

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Interaction/Point ≡ Perturbation (stabilizing or Destabilizing)

ex: Covalent Bond
Ionic Bond
Electrostatic Attraction/Repulsion
Hydrogen bond
dipole-dipole
π–π
hydrophobic
Steric repulsion ← Majority of focus

(19) Catalyst/Ligand Design

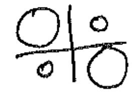
L* – M } cat*

Design Principles:

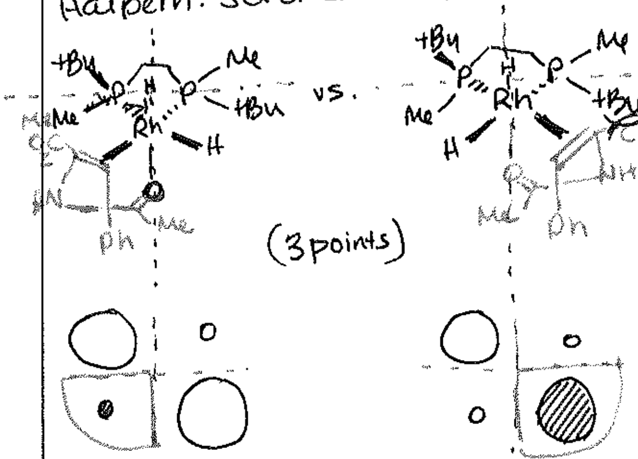
1) Symmetry
often C_2 → Reduce # of geometric possibilities.

L* — M · · · · TS‡

(20) Quadrant Formalism



Recall: Asym H_2-ation example.
Halpern. Science 1982, 217, 401.



(3 points)

Steric repulsion leads to enantio-selectivity

(21)

2) Not easy to depict TS's, so people often look at intermediates.

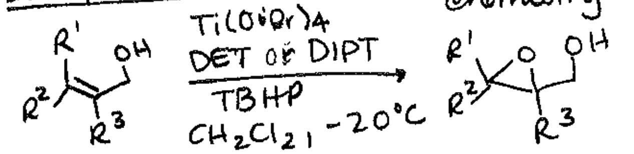
DANGEROUS.

Curtin-Hammett may be at play.

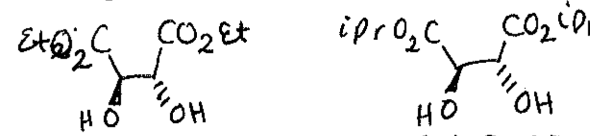
Confirm enantiodetermining step, so you know where to look.
(Kinetics)

(22) Power of Asym Catal (& Mechanistic Analysis)

Sharpless Epoxidation ← Changed org. chemistry



Chiral Ligands:



L-(+)-DET (natural) | L-(+)-DIPT

D-(-)-DET (unnatural) | D-(-)-DIPT

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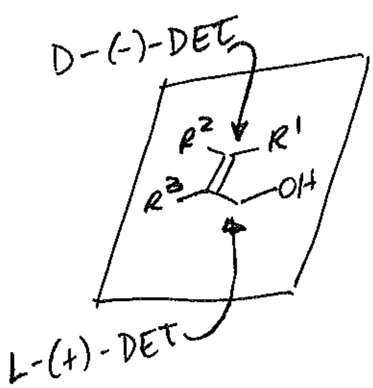
Tough to run:
- Catalyst made in situ
- WATER SENSITIVE

Why so widely used?
1) Readily Available Components
2) Exquisite Exptls.
3) PREDICTABLE

(24)



Regardless of R^1, R^2, & R^3!!

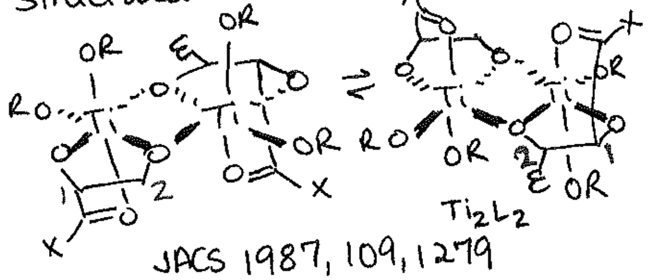
(25) What is mechanism?

"Unexpected diversity" of Ti(tartrate) structures:

5 published X-ray structures

8 different tartrate binding modes!

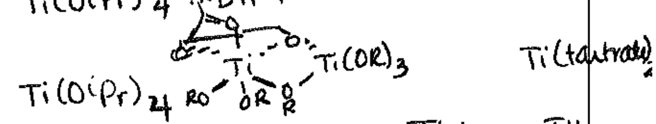
Structures are FLEXIBLE:



JACS 1987, 109, 1279

(26) How is there high ee if multiple catalytic species?

If $Ti(OiPr)_4$: DIPT = 1:1 (CH_2Cl_2)



	Ti_1L_0	Ti_2L_1	Ti_2L_2	TiL_2
fraction	~10%	~10%	~80%	0%
rel rate	0.38	0.28	1	0
ee	none	low	high	--

COMPETING MECHANISMS

LUCKY! Most active catalyst is most selective!

LIGAND-ACCELERATED CATALYSIS

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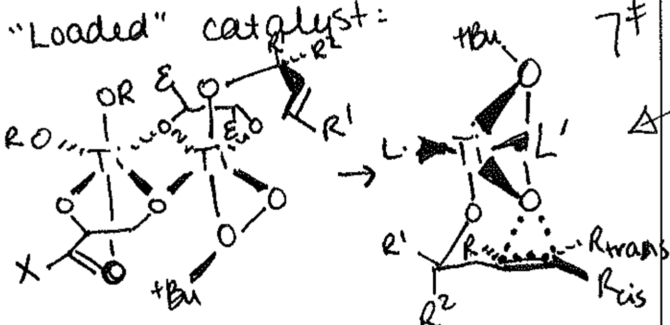
$$\text{rate} \propto \frac{[Ti(tartrate)(OR)_2][TBHP][allylic\ alcohol]}{[ligand\ alcohol]^2}$$

So, we know what's in TS...

"Loaded" catalyst:



"Butterfly Mechanism"

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Computational Analysis (DFT)

Wu JOC 1995, 60, 673;

JACS 1995, 117, 11327.

Rev: Evans. Chem Rev. 1993, 93, 1307.

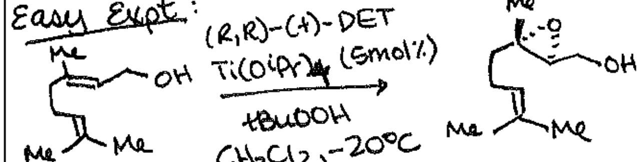
(29) $EE_{prod} = EE_0\, ee_{aux}$ ← linear

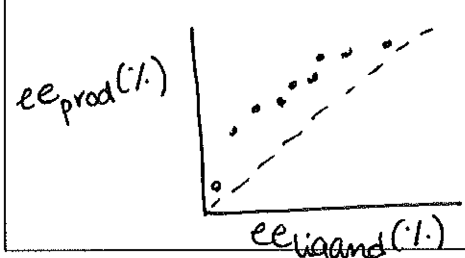
Nonlinear Effects

Kagan JACS 1986, 108, 2353

ACIE 1998, 37, ~~2923~~ 2922.

Easy Expt:





Asymm. Amplification.

Heterochiral catalyst is less reactive than homochiral catalyst.

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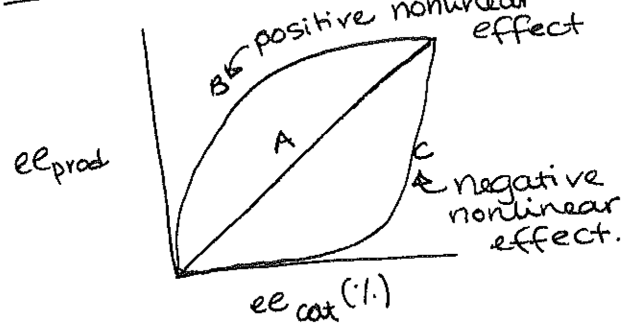
Nonlinear Effect ⇒ Some sort of catalyst aggregation.

Note: No nonlinear ≠ no aggregation



Active Catalyst = Dimer

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ML_2 model:

$$M + L_R + L_S \rightleftharpoons \underset{(x)}{ML_RL_R} + \underset{(y)}{ML_SL_S} + \underset{(z)}{ML_RL_S}$$

ML_RL_R → (EE_0, k_{RR}, +A) → P_R

ML_SL_S → ($-EE_0$, k_{SS}, +A) → P_S

ML_RL_S → (k_{RS}, $EE_0' = \phi$) → $P_{racemic}$

$$EE_{prod} = EE_0 \, ee_{aux} \left(\frac{1+\beta}{1+g\beta} \right)$$

$\beta = \frac{z}{(x+y)}$

$g = k_{RS}/k_{RR}$

EE_0 = ee when only L_R (or L_S) is used.

(32)

$k_{RR} = k_{SS}$

Assume steady state for ML_2 complexes

(33)

Possibilities

1) $B = \phi$ (no ML_RL_S) **or** $g = 1$ (identical rates)

⇓

no NLE

$EE_{prod} = EE_0 \, ee_{aux}$

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2) $g < 1$

Meso less reactive than homochiral

(+)-NLE

3) $g > 1$

Meso more reactive than homochiral

(−)-NLE

(35)

Reservoir Model (Monomeric Active Cat)

$cat_R \cdot cat_R$, $cat_S \cdot cat_S$, $cat_R \cdot cat_S$ ⇌ $cat_R \xrightarrow{A} P_R$

$cat_R \cdot cat_R$, $cat_S \cdot cat_S$, $cat_R \cdot cat_S$ ⇌ $cat_S \xrightarrow{A} P_S$

(36)

$$ee_{eff} = \frac{ee_{aux} - \alpha \, ee_{res}}{1 - \alpha}$$

α = fraction of catalyst in reservoir

if $ee_{res} \neq ee_{aux}$ ⇒ NLE

(+)-NLE : Hetero/meso more stable/less reactive

(−)-NLE : Hetero/meso less stable/more reactive

(37)

How do you know whether it's dimeric active catalyst or reservoir effect?

Cryoscopic MW measurements
kinetics w/ cat of diff %ee.
Study cat in solution

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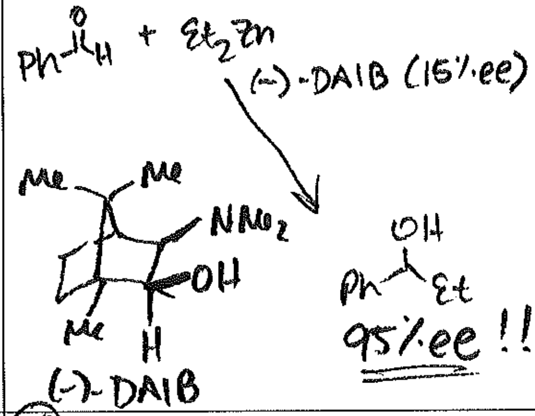
HUGE (+)-NLE :

Noyori et al. JACS 1989, 111, 4028.



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(41)

(42)